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EPIDEMIOLOGY OF PROSTATE CANCER

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Introduction

Prostate cancer is the most common non-skin cancer in most western populations, and although worldwide incidence rates were on the rise through the 1990s,[1] they now appear to be declining slightly.[2] In western countries, the rise in incidence in the late 1970s and early 1980s was due, in part, to the increased use of transurethral resection of the prostate for benign prostatic hyperplasia (BPH).[3] However, the increase in incidence between 1986 and 1992 was largely due to the increasing use of prostate specific antigen (PSA) testing for early detection of prostate cancer.[4] Although incidence rates in Asian countries are low, their recent relative increases are larger than those of western countries and have been attributed to increased westernization.[1]

Despite prostate cancer's high morbidity, its etiology remains obscure. The only established risk factors are age, race and a family history of prostate cancer. Many putative factors, such as hormones, diet, obesity, physical inactivity, occupation, vasectomy, smoking, sexual factors, and genetic susceptibility, have been implicated, but the epidemiologic evidence is inconclusive. An overview of these factors is presented below.

Table 1. Summary of Epidemiologic Risk Factors for Prostate Cancer

	Observation	Evidence	Implications
Established Factors			
Age	Incidence rises with age	Consistent	Latency is long and progression is slow
Race	African-Americans have the highest reported rates in the world, while Chinese men living in China have the lowest reported rates.	Consistent	Suggests both environmental and genetic factors may have a role in prostate cancer
	Migrants have much higher risk than their counterparts in ancestral countries	Consistent	Suggests a role of environmental factors
			Suggests westernization may be related to an increased risk
Family history of prostate cancer	Familial aggregation	Consistent	Suggests a role of genetic predisposition
Probable Factors			
Diet	Animal fat and red meat intake is associated with an increased risk	Somewhat consistent	Suggests fat or other constituents in meat may contribute to prostate carcinogenesis
	Selenium and vitamin E are associated with a reduced risk	Somewhat consistent	Suggests anti-carcinogenic effect of these compounds
			Chemoprevention trials are underway to evaluate these effects
	Consumption of tomato products is associated with a decreased risk	Somewhat consistent	Lycopene may protect against prostate cancer

Table 1 (*Continued*)

	Intake of cruciferous vegetables may be associated with decreased risk	Suggestive	Suggests intake of broccoli, cauliflower, Brussels sprouts and other cruciferous vegetables may protect against prostate cancer
	Allium vegetable intake may be associated with decreased risk	Needs confirmation	
	Intake of fish and marine fats may be associated with a decreased risk	Needs confirmation	
	Calcium may be associated with	Inconsistent	

Table 1 (*Continued*)

	Intake of cruciferous vegetables may be associated with decreased risk	Suggestive	Suggests intake of broccoli, cauliflower, Brussels sprouts and other cruciferous vegetables may protect against prostate cancer
	Allium vegetable intake may be associated with decreased risk	Needs confirmation	
	Intake of fish and marine fats may be associated with a decreased risk	Needs confirmation	
	Calcium may be associated with increased risk	Inconsistent	
	Intake of total vegetables may be associated with decreased risk	Inconsistent	
IGFs	Higher serum/plasma levels of IGF-I and lower levels of IGFBP-3 may be related to an increased risk	Somewhat consistent	Suggests IGFs may be related to the progression of prostate cancer Clinical utility of IGFs is under evaluation
Occupation	Farmers have ~10% excess risk	Consistent	Suggests exposures to herbicides or pesticides or lifestyles among farmers may be related to prostate cancer risk
	Workers in heavy metal and rubber industries may have an increased risk	Suggestive	Suggests exposures to certain chemicals may increase prostate cancer risk
Androgens	Higher serum levels of androgens may be associated with an increased risk	Suggestive	Suggests androgenic action is involved in prostate carcinogenesis
Obesity	Abdominal obesity may be related to an increased risk	Suggestive	Suggests that alteration of hormone synthesis or metabolism may have a role in prostate cancer etiology

Table 1 (*Continued*)

	Observation	Evidence	Implications
Chronic inflammation	Inflammation is found in prostate biopsies and resected prostate tissue, and pro-inflammatory markers are associated with increased risk	Suggestive	Suggests that factors contributing to inflammatory states may have a role in prostate cancer initiation or promotion
Vitamin D	Higher serum levels of vitamin D may be associated with a reduced risk	Inconsistent	
Sexual factors	Sexual factors, especially sexually transmitted infections such as HPV infection and syphilis, may be related to an increased risk	Inconsistent	
Vasectomy	Vasectomy may be associated with an increased risk	Inconsistent	
Physical activity	Long-term physical activity may be associated with a reduced risk of prostate cancer	Inconsistent	
Liver cirrhosis	Patients with liver cirrhosis may have a lower risk	Inconsistent	
Diabetes	Diabetic patients may have a lower risk	Inconsistent	
Smoking	Smoking may be associated with an increased risk	Inconsistent	

Table 2. Summary of Epidemi

Region	Gene	Markers
1q24-25	*RNASEL* (HPC1)	E265X, R462Q, D541E, I97L
17p11	*ELAC2* (HPC2)	A541T, S217L

*HPC: Hereditary prostate cancer.

Table 2. Summary of Epidemiologic Studies of Rare, High Penetrance Genes, and Prostate Cancer

Region	Gene	Markers	Studies (Ref.), No. of cases Studied, Population	Results
1q24-25	*RNASEL* (HPC1)	E265X, R462Q, D541E, I97L	Rokman *et al.* (2002),[75] N=116 HPC* cases, Finns	Positive association
			Nakazato *et al.* (2003),[76] N=101 HPC cases, Japanese	Positive association
			Wang *et al.* (2002),[77] N=438 HPC cases, US Caucasians	Positive association
			Casey *et al.* (2002),[78] N=423 HPC cases, US subjects	Positive association
				Overall, consistent positive association
17p11	*ELAC2* (HPC2)	A541T, S217L	Rebbeck *et al.* (2000),[79] N = 359 cases, US subjects	Positive association
			Suarez *et al.* (2001),[80] N = 257 HPC cases, US Caucasians	Positive association
			Tavtigian *et al.* (2001),[81] N = 429 HPC cases, US Caucasians	Positive association
			Vesprini *et al.* (2001),[82] N = 431 cases, Canadians	No association
			Wang *et al.* (2001),[83] N = 446 HPC cases, US Caucasians	No association
			Xu *et al.* (2001),[84] N = 249 cases, 159 HPC cases, US Caucasians	No association
			Rokman *et al.* 2001,[85] N = 467 cases, 107 HPC cases, Finns	No association
			Meitz *et al.* (2002),[86] N = 432 cases, UK subjects	No association
			Adler *et al.* (2003),[87] N = 199 cases, Canadians	Positive association

*HPC: Hereditary prostate cancer.

Table 2 (*Continued*)

Region	Gene	Markers	Studies (Ref.), No. of cases Studied, Population	Results
			Stanford *et al.* (2003),[88] N = 591 cases, US subjects	Positive association
			Takahashi *et al.* (2003),[89] N = 98 cases (BPH controls), Japanese	Positive association
			Severi *et al.* (2003),[90] N = 825 cases, Australians	No association
			Meta-analysis: Camp and Tavtigian (2002)[91]	Association only for HPC Overall, weak, inconsistent associations
				May be associated only with HPC, not sporadic disease
xq27-28	None (HPCX)		Linkage studies	AR (also on X chromosome) unlikely to be HPCX susceptibility gene
20q13	None (HPC20)		Linkage studies	Linkage studies need further confirmation
1p36	None (CAPB)		Linkage studies	Most consistent linkage to strong family history with early onset disease
1q42.2-43	PCTA-1 (PCAP)		Linkage studies	PCTA is possible candidate gene, but no functional markers
8p22-23	MSR1	PRO3, P275A, D174Y, IVS5-59, R293X	Xu *et al.* (2003),[92] N = 301 cases, US Caucasians	Positive association
			Miller *et al.*, 2003,[93] N = 134 cases, African-Americans	Positive association

Table 2 (*Continued*)

Region	Gene	Markers	Studies (Ref.), No. of cases Studied, Population	Results
			Wang *et al.* (2003),[94] N = 499 cases, 438 HPC cases, US Caucasians	Null association
			Seppala *et al.* (2003),[95] N = 537 cases, Finns	Null association
				Overall, weak results, with larger studies showing null associations even for HPC

Rates and Patterns

Incidence

There is considerable variation in reported incidence rates of prostate cancer worldwide.[5,6] Age-adjusted prostate cancer incidence rates among African-Americans are the highest in the world (185.4 per 100,000 person-years), and rates among Caucasian-Americans are second (107.8 per 100,000 person-years) (Fig. 1). Reported rates in the Caribbean and in Brazil, where there are large populations of African descent (92–96 per 100,000 person-years), are comparable to the high rates among Caucasian-Americans. In contrast, in Central America and other parts of South America, rates are much lower (28–42 per 100,000 person-years). Rates within Europe vary almost seven-fold (from 15–100 per 100,000 person-years), with Austria having the highest reported rates. Although rates in Canada, Oceania (including Australia and New Zealand), Western Europe and Scandinavia (50–103 per 100,000 person-years) are generally not as high as the rates reported in the US, they are 2–3 times higher than rates in Eastern Europe (15–36 per 100,000 person-years). Within Asia, where the rates are the lowest, there is also considerable variation in reported incidence, with more westernized Asian countries such as Israel and the Philippines (22–47 per 100,000 person-years) showing markedly

Table 3. Summary of Epidemiologic Studies of Common, Low Penetrance Genes and Prostate Cancer

Gene	Marker	Studies (Ref.), No. of Cases Studied, Population	Results and Comments
Androgen Biosynthesis/Metabolism Pathway			
CYP17	MspA1	Lunn *et al.* (1999),[120] N = 108 cases, US subjects	Positive association for Caucasians, null for African-Americans
		Wadelius *et al.* (1999),[134] N = 178 cases, Swedish Caucasians	Positive association
		Gsur *et al.* (2000),[135] N = 63 cases, Austrians	Positive association
		Habuchi *et al.* (2000),[136] N = 252 cases, Japanese	Positive association
		Haiman *et al.* (2001),[137] N = 600 cases, US Caucasians	Null association
		Yamada *et al.* (2001),[125] N = 105 cases, Japanese	Positive association
		Kittles *et al.* (2001),[138] N = 71 cases, African-Americans	Positive association
		Latil *et al.* (2001),[110] N = 226 cases, French Caucasians	Null association
		Chang *et al.* (2001),[139] N = 225 cases, US Caucasians	Null association
		Stanford *et al.* (2002),[140] N = 596 cases, US Caucasians and African-Americans	Null association overall, positive association among Caucasians with family history
		Madigan *et al.* (2003),[141] N = 174 cases, Chinese	Null association
		Lin *et al.* (2003),[142] N = 93 cases, Taiwanese	Null association
		Nam *et al.* (2003),[119] N = 483 cases, Canadians	Null association
		Review: Ntais *et al.* (2003)[98]	Meta-analysis indicates no overall association, but A2 allele may be associated with risk in African-Americans.[98] A1 is reported to be risk allele in Asians.

Table 3 (*Continued*)

CYP19	TTTA repeats, N264C	Latil *et al.* (2001),[110] N = 226 cases, French Caucasians	Positive association
		Modugno *et al.* (2001),[111] N = 88 cases, US Caucasians	Positive association
		Suzuki *et al.* (2003),[143] N = 99 HPC* cases, Japanese	Positive association
			Overall, suggestive but mixed results — longer TTTA alleles associated with higher risk in Caucasians, but lower risk in Asians. Further investigation needed.

Table 3 (*Continued*)

CYP19	TTTA repeats, N264C	Latil *et al.* (2001),[110] N = 226 cases, French Caucasians	Positive association
		Modugno *et al.* (2001),[111] N = 88 cases, US Caucasians	Positive association
		Suzuki *et al.* (2003),[143] N = 99 HPC* cases, Japanese	Positive association
			Overall, suggestive but mixed results — longer TTTA alleles associated with higher risk in Caucasians, but lower risk in Asians. Further investigation needed.
CYP1A1	2455A>G	Murata *et al.* (1998),[144] N = 115 cases, Japanese	Positive associaton
	3801T>C	Suzuki *et al.* (2003),[145] N = 81 HPC cases, Japanese	Positive association
	2453C>A	Chang *et al.* (2003),[146] N = 245 cases, US Caucasians	Positive association
CYP3A4	5′ promoter variant	Rebbeck *et al.* (1998),[147] N = 230 cases, US Caucasians	Positive association
		Paris *et al.* (1999),[148] N = 174 cases, African-Americans	Positive association
		Nam *et al.* (2003),[119] N = 483 cases, Canadians	Null association
SRD5A2	V89L, A49T, R227Q, TA repeats	Lunn *et al.* 1999,[120] N = 108 cases, US Caucasians and African-Americans	Null association
		Kantoff *et al.* (1997),[121] N = 590 cases, US Caucasians	Null association
		Febbo *et al.* (1999),[122] N = 592 cases, US Caucasians	Null association
		Makridakis *et al.* (1999),[123] N = 388 cases, US Hispanics and African-Americans	Positive association

*HPC: Hereditary prostate cancer.

Table 3 (*Continued*)

Gene	Marker	Studies (Ref.), No. of Cases Studied, Population	Results and Comments
		Margiotti *et al.* (2000),[124] N = 108 cases, Italians	Positive association
		Yamada *et al.* (2001),[125] N = 105 cases, Japanese	Null association
		Nam *et al.* (2001),[126] N = 158 cases, Canadians	Positive association
		Latil *et al.* (2001),[110] 226 cases, French	Null association
		Mononen *et al.* (2001),[127] N = 449 cases, Finns	Null association
		Hsing *et al.* (2001),[128] N = 191 cases, Chinese	Null association
		Pearce *et al.* (2002),[129] N = 921 cases, US subjects	Null association
		Soderstrom *et al.* (2002),[130] N = 176 cases, Swedes	Null association
		Lamharzi *et al.* (2003),[131] N = 300 cases, US subjects	Positive association
		Chang *et al.* (2003),[132] N = 245 cases, 159 HPC cases, US Caucasians	Null association
		Li *et al.* (2003),[133] N = 302 cases, Japanese	Positive association
		Nam *et al.* (2003),[119] N = 483 cases, Canadians	Null association
		Review: Ntais *et al.* (2003)[96]	Overall, the T allele of A49T (associated with higher enzymatic activity) and shorter TA repeats may be associated with a modest increase in risk.[96] While results are mixed, the V89L marker's LL genotype, which is associated with lower serum levels of androgens, may be associated with a reduced risk. R227Q is very rare, observed only in Asians.

Table 3 (*Continued*)

AR	CAG repeats, GGN repeats	Ingles *et al.* (1997),[100] N = 57 cases, US Caucasians	Positive association
		Stanford *et al.* (1997),[101] N = 301 cases, US Caucasians	Positive association
		Giovannucci *et al.* (1997),[102] N = 587 cases, US Caucasians (and Platz *et al.* (1998),[103] N = 582 cases)	Positive association
		Correa-Cerro *et al.* (1999),[104] N = 132 cases, French and Germans	Null association
		Ekman *et al.* (1999),[105] N = 93 cases, 59 HPC cases, Swedes and Japanese	Positive association
		Edwards *et al.* (1999),[106] N = 178 cases,	Positive association

Table 3 (*Continued*)

AR	CAG repeats, GGN repeats	Ingles *et al.* (1997),[100] N = 57 cases, US Caucasians	Positive association
		Stanford *et al.* (1997),[101] N = 301 cases, US Caucasians	Positive association
		Giovannucci *et al.* (1997),[102] N = 587 cases, US Caucasians (and Platz *et al.* (1998),[103] N = 582 cases)	Positive association
		Correa-Cerro *et al.* (1999),[104] N = 132 cases, French and Germans	Null association
		Ekman *et al.* (1999),[105] N = 93 cases, 59 HPC cases, Swedes and Japanese	Positive association
		Edwards *et al.* (1999),[106] N = 178 cases, U.K. Caucasians	Positive association
		Hsing *et al.* (2000),[107] N = 190 cases, Chinese	Positive association
		Miller *et al.* (2001),[108] N = 140 cases, US subjects	Null association
		Beilin *et al.* (2001),[109] N = 445 cases, Australians	Null association
		Latil *et al.* (2001),[110] N = 226 cases, French	Null association
		Modugno *et al.* (2001),[111] N = 88 cases, US Caucasians	Positive association
		Chang *et al.* (2002),[112] N = 245 cases, 159 HPC cases	Positive association
		Mononen *et al.* (2002),[113] N = 449 cases, Finns	Positive association
		Gsur *et al.* (2002),[114] N = 190 cases, Austrians	Null association
		Chen *et al.* (2002),[115] N = 300 cases, US subjects	Null association
		Balic *et al.* (2002),[116] N = 82 cases, Hispanics	Positive association
		Santos *et al.* (2003),[117] N = 133 cases, Brazilians	Null association
		Huang *et al.* (2003),[118] N = 66 cases, Taiwanese	Null association
		Nam *et al.* (2003),[119] N = 483 cases, Canadians	Null association
			Although overall results are mixed, shorter CAG repeat lengths may be associated with increased prostate cancer risk.

Table 3 (*Continued*)

Gene	Marker	Studies (Ref.), No. of Cases Studied, Population	Results and Comments
HSD3B1	N367T, c7062t	Chang *et al.* (2002),[149] N = 245 cases, 159 HPC cases, US Caucasians	Positive association
HSD3B2	c7159g, c7474t	Chang *et al.* (2002),[149] N = 245 cases, 159 HPC cases, US Caucasians	Null association
HSD17B3	G289S	Margiotti *et al.* (2002),[150] N = 103 cases, Italians	Positive association
Growth Factors and Non-androgenic Hormone Pathways			
VDR	BsmI, TaqI, polyA, ApaI, FokI	Taylor *et al.* (1996),[154] N = 108 cases, US Caucasians	Positive association
		Ingles *et al.* (1997),[100] N = 57 cases, US Caucasians	Positive association
		Ingles *et al.* (1998),[155] N = 151 cases, African-Americans	Null association
		Ma *et al.* (1998),[156] N = 372 cases, US Caucasians	Null association
		Correa-Cerro *et al.* (1999),[157] N = 131 cases, Europeans	Null association
		Habuchi *et al.* (2000),[158] N = 222 cases, Japanese	Positive association
		Furuya *et al.* (1999),[159] N = 66 cases, Japanese	Null association
		Watanabe *et al.* (1999),[160] N = 100 cases, Japanese	Null association
		Blazer *et al.* (2000),[161] N = 77 cases, US Caucasians	Null association
		Chokkalingam *et al.* (2001),[162] N = 191 cases, Chinese	Null association
		Gsur *et al.* (2002),[163] N = 190 cases, Austrians	Null association
		Hamasaki *et al.* (2002),[164] N = 110 cases, Japanese	Positive association for aggressive disease
		Medieros *et al.* (2002),[165] N = 163 cases, Portugese	Positive association for late-onset disease
		Suzuki *et al.* (2003),[166] N = 81 HPC cases, Japanese	Null association
		Nam *et al.* (2003),[119] N = 483 cases, Canadians	Null association

Table 3 (*Continued*)

		Review: Ntais *et al.* (2003)[97]	Overall, meta-analysis[97] shows null association for all markers. 3′ markers (BsmI, Taq1, ApaI and polyA) are non-functional, 5′ FokI marker is functional.
INS	+1127PstI	Ho *et al.* (2003),[153] N = 126 cases, US subjects	Positive association
TH	−4217PstI	Ho *et al.* (2003),[153] N = 126 cases, US subjects	Null association
IGF-1	CA repeats	Nam *et al.* (2003),[119] N = 483 cases, Canadians	Positive association
IGF-2	MspI	Ho *et al.* (2003),[153] N = 126, US subjects	Null association
IGFBP-3	−202A/C	Wang *et al.* (2003),[94] N = 307 cases, Japanese	Null association
		Nam *et al.* (2003),[119] N = 483 cases, Canadians	Null association

Table 3 (*Continued*)

		Review: Ntais *et al.* (2003)[97]	Overall, meta-analysis[97] shows null association for all markers. 3′ markers (BsmI, Taq1, ApaI and polyA) are non-functional, 5′ FokI marker is functional.
INS	+1127PstI	Ho *et al.* (2003),[153] N = 126 cases, US subjects	Positive association
TH	−4217PstI	Ho *et al.* (2003),[153] N = 126 cases, US subjects	Null association
IGF-1	CA repeats	Nam *et al.* (2003),[119] N = 483 cases, Canadians	Positive association
IGF-2	MspI	Ho *et al.* (2003),[153] N = 126, US subjects	Null association
IGFBP-3	−202A/C	Wang *et al.* (2003),[94] N = 307 cases, Japanese	Null association
		Nam *et al.* (2003),[119] N = 483 cases, Canadians	Null association
Carcinogen Metabolism Pathway			
GSTT1	Deletion	Medeiros *et al.* (2004),[167] N = 150 cases, Portugese	Null association
		Nakazato *et al.* (2003),[76] N = 81 cases, Japanese	Null association
		Kidd *et al.* (2003),[168] N = 206 cases, Finns	Null association
		Kote-Jarai *et al.* (2001),[169] N = 275 cases, U.K. Caucasians	Null association
		Gsur *et al.* (2001),[170] N = 166 cases, Austrians	Null association
		Murata *et al.* (2001),[171] N = 115 cases, Japanese	Null association
		Steinhoff *et al.* (2000),[172] N = 91 cases, Germans	Positive association
		Autrup *et al.* (1999),[173] N = 153 cases, Dutch subjects	Null association
		Nam *et al.* (2003),[119] N = 483 cases, Canadians	Positive association
		Kelada *et al.* (2000),[174] N = 276 cases, US subjects	Positive association
GSTM1	Deletion	Medeiros *et al.* (2004),[167] N = 150 cases, Portugese	Null association
		Nakazato *et al.* (2003),[76] N = 81 cases, Japanese	Null association
		Kidd *et al.* (2003),[168] N = 206 cases, Finns	Positive association
		Kote-Jarai *et al.* (2001),[169] N = 275 cases, U.K. Caucasians	Null association

Table 3 (*Continued*)

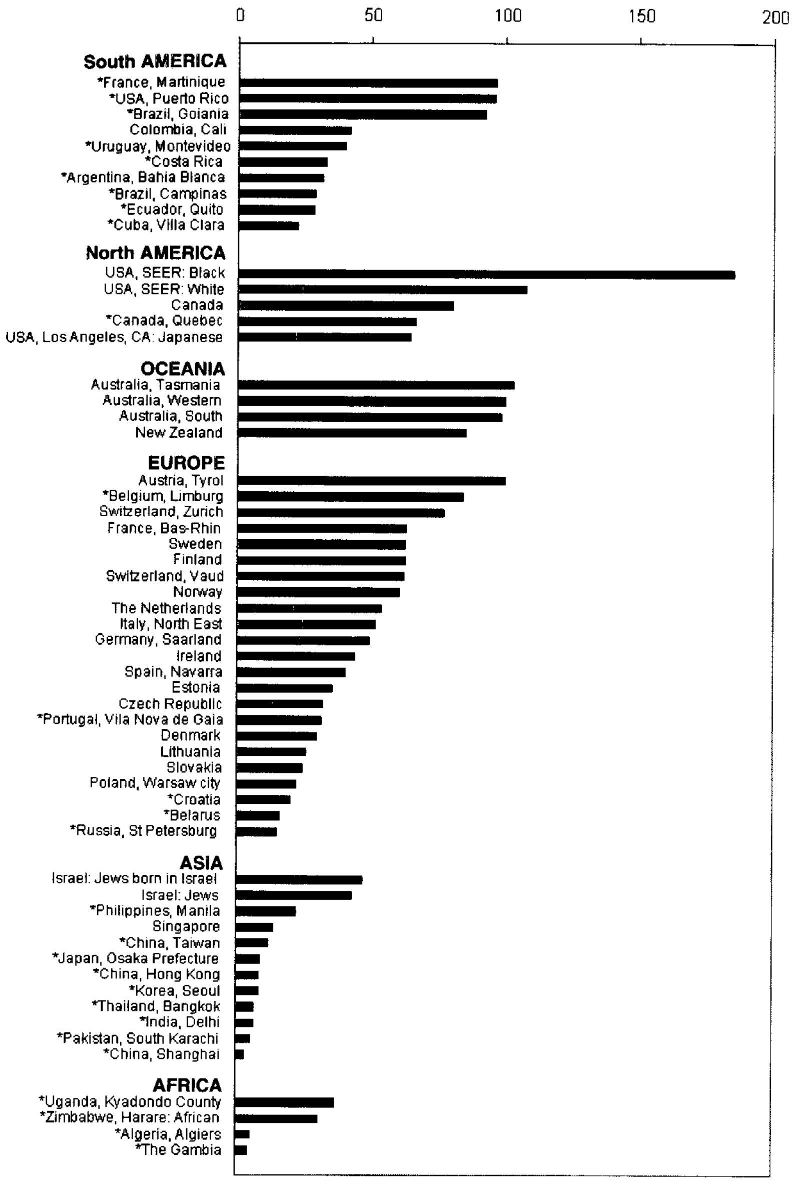
Gene	Marker	Studies (Ref.), No. of Cases Studied, Population	Results and Comments
		Gsur *et al.* (2001),[170] N = 166 cases, Austrians	Null association
		Murata *et al.* (2001),[171] N = 115 cases, Japanese	Positive association
		Steinhoff *et al.* (2000),[172] N = 91 cases, Germans	Null association
		Autrup *et al.*, 1999,[173] N = 153 cases, Dutch subjects	Null association
		Nam *et al.* (2003),[119] N = 483 cases, Canadians	Null association
		Kelada *et al.* (2000),[174] N = 276 cases, US subjects	Null association
GSTM3		Medeiros *et al.* (2004),[167] N = 150 cases, Portugese	Positive association
GSTP1	I105V	Nakazato *et al.* (2003),[76] N = 81 cases, Japanese	Positive association
		Kidd *et al.* (2003),[168] N = 206 cases, Finns	Null association
		Kote-Jarai *et al.* (2001),[169] N = 275 cases, U.K. Caucasians	Positive association
		Gsur *et al.* (2001),[170] N = 166 cases, Austrians	Positive association
		Steinhoff *et al.* (2000),[172] N = 91 cases, Germans	Null association
		Shepard *et al.* (2000),[175] N = 590 cases, US Caucasians	Null association
		Autrup *et al.* (1999),[173] N = 153 cases, Dutch	Null association
		Wadelius *et al.* (1999),[134] N = 850 subjects, Swedes and Danes	Null association
		Nam *et al.* (2003),[119] N = 483 cases, Canadians	Null association
NAT2		Wadelius *et al.* (1999),[134] N = 850 subjects, Swedes and Danes	Null association
DNA Repair Pathway			
XRCC1	R399Q, R194W, R280H	Rybicki *et al.* (2004),[177] N = 637 cases, US Caucasians	Null association
		van Gils *et al.* (2002),[178] N = 77 cases, US subjects	Positive association

Table 3 (*Continued*)

XPD	D312N, K751Q	Rybicki *et al.* (2004),[177] N = 637 cases, US Caucasians	Positive association, needs further investigation
hOGG1	S326C, +11657A/G	Xu *et al.* (2002),[179] N = 245 cases, US Caucasians	Positive association
		Chen *et al.* (2003),[180] N = 84 cases, US Caucasians	Positive association
Inflammation/Angiogenesis/Cytokine Pathways			
VEGF	VEGF-1154, VEGF-460	McCarron *et al.* (2002),[183] N = 247 cases, U.K. Caucasians	Positive association
		Lin *et al.* (2003),[142] N = 96 cases, Taiwanese	Positive association

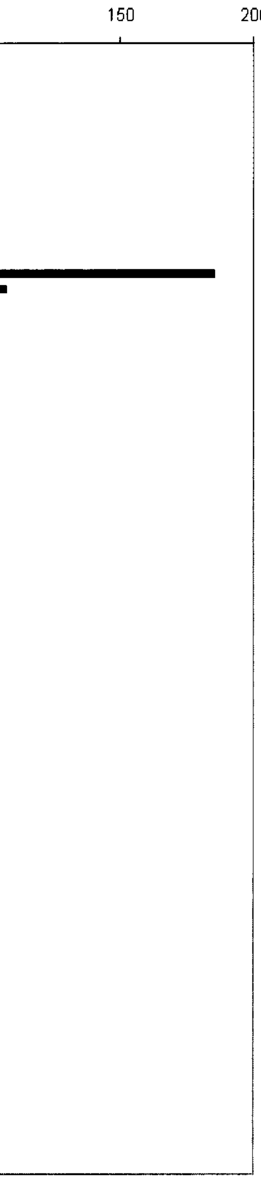
Table 3 (*Continued*)

XPD	D312N, K751Q	Rybicki *et al.* (2004),[177] N = 637 cases, US Caucasians	Positive association, needs further investigation
hOGG1	S326C,	Xu *et al.* (2002),[179] N = 245 cases, US Caucasians	Positive association
	+11657A/G	Chen *et al.* (2003),[180] N = 84 cases, US Caucasians	Positive association
Inflammation/Angiogenesis/Cytokine Pathways			
VEGF	VEGF-1154, VEGF-460	McCarron *et al.* (2002),[183] N = 247 cases, U.K. Caucasians	Positive association
		Lin *et al.* (2003),[142] N = 96 cases, Taiwanese	Positive association
TNF-α	TNF-α-308	McCarron *et al.* (2002),[183] N = 247 cases, U.K. Caucasians	Null association
IL-1-β	IL-1β-511	McCarron *et al.* (2002),[183] N = 247 cases, U.K. Caucasians	Null association
IL-8	IL-8-251	McCarron *et al.* (2002),[183] N = 247 cases, U.K. Caucasians	Positive association
IL-10	IL-10-1082	McCarron *et al.* (2002),[183] N = 247 cases, U.K. Caucasians	Positive association
PPAR-γ	P12A	Paltoo *et al.* (2003),[184] N = 193 cases, Finns	Null association
TGF-β	L10P	Li *et al.* (2004),[181] N = 351 cases, Japanese	Positive association
COX-2	−1285A/G −1265G/A −899G/C −297C/G	Panguluri *et al.* (2004),[182] N = 288, 264 and 184 cases, African-Americans, Nigerians, and US Caucasians	Positive association in all ethnic groups



Source: Parkin DM, Whelan SL, Ferlay J, Teppo L, and Thomas DB. Cancer Incidence in Five Continents, Vol VIII, IARC Sci Publ 155, 2003.

Fig. 1. Age-adjusted incidence rates (per 100,000 person-years) for prostate cancer in 48 countries, 1993–1997.



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RC Sci Publ 155, 2003.

on-years) for prostate cancer in

higher rates than Thailand, India, Pakistan and Shanghai, China (3–7 per 100,000 person-years). There are few data on incidence in Africa, with only four registries included in the IARC report.[6] The rates within the African continent vary widely, from 5–37 per 100,000 person-years. Part of the difference in incidence rates in various countries is related to the extent of prostate cancer screening, especially the use of prostate-specific antigen (PSA) testing. However, since screening is less common in developing countries, it is not likely to explain the nearly 60-fold difference in prostate cancer risk between high- and low-risk populations.

Mortality

In the US, only one in six men diagnosed with prostate cancer will eventually die from it. Nevertheless, 29,900 prostate cancer deaths are expected in 2004, making prostate cancer the second leading cause of cancer death among US men after lung cancer.[7] Age-adjusted prostate cancer mortality rates from 38 countries in 1998 are shown in Fig. 2. Overall, mortality patterns mimic those of incidence in various countries, although mortality rates show less diversity worldwide than do incidence rates, but are still higher in Western nations than in lower-risk, Asian countries (Fig. 2). Of special interest is the observation that the Caribbean nations of Barbados, the Bahamas and Trinidad and Tobago, where there are large populations of men of African descent, had the world's highest mortality rates (30.3 to 47.9 per 100,000 person-years). Mortality was higher in Scandinavian countries and parts of northern Europe than in the US (18.7–23.6 versus 14.0 per 100,000 person-years), and lowest of all in the Asian countries of South Korea, Philippines and Japan (1.6–4.4 per 100,000 person-years).

Risk Factors

Demographic Factors

Age

Over 80% of prostate tumors in the US are diagnosed among men over age 65,[8] and the incidence of prostate cancer increases exponentially

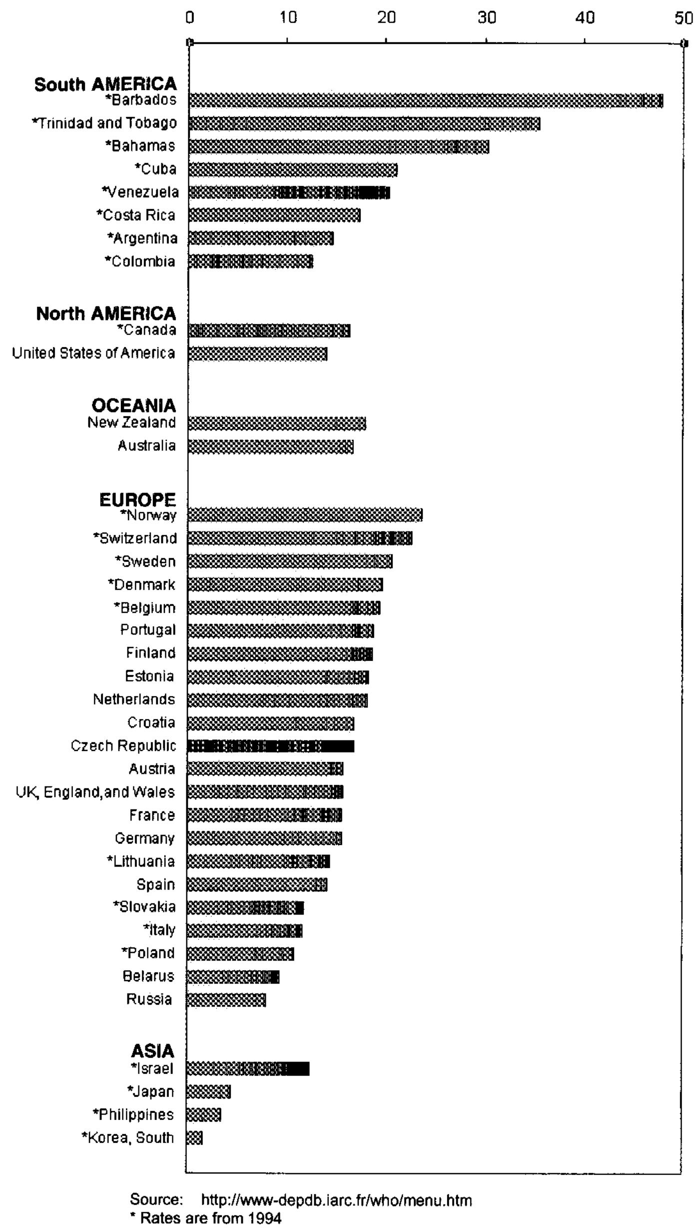
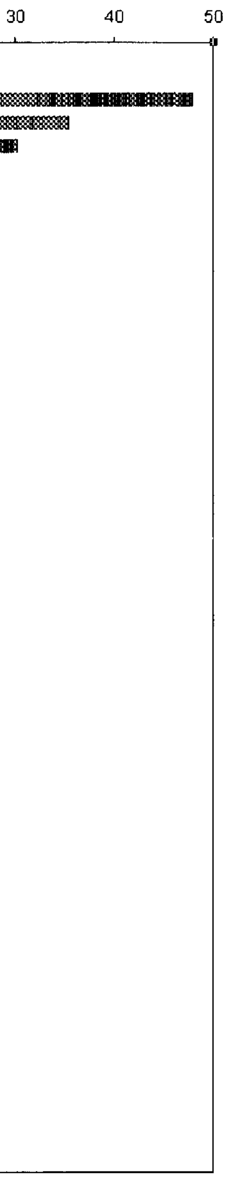


Fig. 2. Age-adjusted mortality rates (per 100,000 person-years) for prostate cancer in 38 countries, 1998.



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with advancing age — an increase that is faster than that for any other malignancy (Table 1). Estimates from the Surveillance, Epidemiology, and End Results (SEER) program from 1996–2000 indicate that for US men under 65 years of age and 65 years and over, age-adjusted prostate cancer incidence rates were 56.8 and 974.7 per 100,000 person-years, respectively.[2]

Racial/Ethnic Variation

Another consistently observed but poorly understood risk factor is ethnicity. African-Americans have the highest incidence rate in the world, roughly 60 times that of the ethnic group with the world's lowest rates, in Shanghai, China[1] (Fig. 1).

Adjustment of incidence rates for prevalence of latent disease at autopsy and proportion of localized tumors among all cancers of the prostate revealed that Japanese men still experience a markedly lower incidence than Americans, indicating that the international variation cannot be explained by differences in detection alone.[9] This bolsters the results of migrant studies suggesting that ethnic factors, including genetic, lifestyle, and environmental factors, may affect prostate cancer risk and explain many of the differences in risk between high- and low-risk populations.[9,10]

Hormonal, Behavioral and Lifestyle Factors

Hormones and Growth Factors

Androgens play a key role in the development and maintenance of the prostate gland; however, the precise role of androgens in the etiology of prostate cancer is unclear. Prostate cancer is notably absent in castrated men, and laboratory studies show that administration of testosterone induces prostate cancer in rats and that androgens promote cell proliferation and inhibit prostate cell death.[11–13] However, epidemiologic data supporting a role of androgens are inconclusive.[14–16] To date, over 13 prospective studies have investigated the role of circulating androgens, and only one was able to show that men with higher serum testosterone levels have a higher risk of prostate cancer.[17] More comprehensive reviews of this topic are reported elsewhere.[14–16] Studies of genetic markers involved in the androgen pathways offer further insight into this avenue of research, and are reviewed later in this chapter.

In addition to androgens, insulin-like growth factors (IGFs), insulin and vitamin D have been implicated in prostate cancer. IGF-I and IGF-II are polypeptides that function as both tissue growth factors and endocrine hormones with mitogenic and anti-apoptotic effects on prostate epithelial cells. There are at least six known IGF binding proteins (IGFBPs) that can bind to IGFs and thus prevent activation of the IGF receptor, which mediates IGF effects. At least nine epidemiologic studies have evaluated the roles of the IGF axis in prostate cancer, and most have reported a positive association with IGF-I and an inverse association with IGFBP3.[18,19] However, the role of IGF-II is less clear.

Vitamin D is a steroid hormone obtained primarily from dermal synthesis in response to sunlight exposure. Vitamin D and its analogs have potent anti-proliferative, pro-differentiative, and pro-apoptotic effects on prostate cancer cells. In addition, vitamin D inhibits prostate tumor growth *in vivo*. In general, laboratory data are consistent and support the hypothesis that vitamin D may protect against prostate cancer. However, results from epidemiologic studies investigating serum vitamin D levels have been inconsistent.[20] The reasons for these conflicting results are unclear.

Diet

Ecologic studies have shown a strong correlation between the incidence of prostate cancer and dietary fat intake.[21] A western diet has been linked to a higher risk of prostate cancer, and it has been suggested that the western diet, high in fat, increases production and availability of both androgen and estrogen, while Asian (low-fat, high-fiber) and vegetarian diets lead to lower circulating levels of these hormones.[21]

Fat is the most studied dietary factor in relation to prostate cancer. Most epidemiologic studies have investigated the role of total, saturated, and/or animal fat. Findings from these studies suggest a possible positive association with monounsaturated, animal and saturated fats, and an inverse association with omega-3 fat. The results for polyunsaturated fat are less consistent.[22,23] Consumption of meat, particularly red meat, is also consistently linked to an increased risk of prostate cancer. However, it is unclear whether the excess risk is due to the fat content in red meat, mutagens such as heterocyclic amines that are induced during high-temperature cooking of meat products, animal proteins, or other unidentified factors.[24]

Several epidemiologic studies have also investigated whether intake of fatty fish, rich in potentially tumor-inhibitory marine fatty acids, is associated with reduced prostate cancer risk. However, a recent review of 17 studies, including eight prospective studies, found suggestive but inconsistent results, possibly due to inadequate assessment of fish intake or lack of information on specific marine fatty acids, particularly the polyunsaturated fatty acids eicosapentaenoic and docosahexaenoic acids,[25] in these studies.

Although consumption of fruits and vegetables is associated with a reduced risk of several cancers, their role in prostate cancer is less clear. The only consistent finding is an inverse association with consumption of tomatoes and tomato paste, which has been largely attributed to the antioxidant effect of lycopene.[26] Cruciferous and allium vegetables have been implicated. A recent review concluded that there is modest evidence that intake of cruciferous vegetables, including broccoli, cabbage, cauliflower, and Brussels sprouts, is inversely associated with prostate cancer risk, possibly due to their content of isothiocyanates.[27] Intake of allium vegetables, including onions, garlic, and chives, was associated with a reduced risk in a case-control study in China.[28] This protective effect may be due to the tumor inhibitory properties of organosulfur compounds.

Dietary calcium, from either dairy intake or supplements, has also been linked to prostate cancer. Because of its role in regulation of vitamin D synthesis, calcium may down-regulate vitamin D's anti-proliferative effects on prostate cancer. However, the epidemiologic evidence for calcium is as yet unclear, complicated by differences in assessment of calcium (dietary intake versus circulating levels).[29] Recent data suggest a threshold effect in that only very high calcium intake (≥ 2000 mg/day) appears to be associated with disease.[30]

Chronic excess of zinc, another mineral obtained largely through dietary supplements, may be positively associated with prostate cancer risk, although *in vitro* studies demonstrating mitogenic effects of zinc on prostate cancer suggest that it may reduce risk.[31]

A large body of epidemiological evidence, including observational, case-control, cohort and randomized controlled clinical trials, supports the hypothesis that selenium may prevent prostate cancer in humans.[32] Molecular data show that selenium prevents clonal expansion of tumors by causing cell cycle arrest, promoting apoptosis, and modulating p53-dependent DNA repair mechanisms. Clinical trials have also shown that vitamin E supplementation is associated with a reduced risk of prostate cancer.[33,34] Currently a clinical trial is under way to test the chemopreventive efficacy of these two compounds.[35]

Obesity

In epidemiologic studies, overall obesity is usually measured by body mass index (weight in kg divided by the square of height in meters, kg/m^2) and abdominal obesity by the ratio of waist to hip circumference. The findings on overall obesity are mixed. However, recent data suggest that abdominal obesity may be associated with an increased risk of prostate cancer even in relatively lean men.[36,37] In addition, higher serum levels of insulin were associated with an increased risk of prostate cancer in China,[38] and higher serum levels of leptin were associated with larger tumor volume ($> 5\ cm^3$).[39] Although the role of obesity in prostate cancer is not clearly defined, future studies should attempt to clarify it further because obesity is linked to numerous putative risk factors for prostate cancer, including high intakes of meat and fat intake, hormone metabolism, and serum level IGFs and insulin. Furthermore, the prevalence of obesity correlates with prostate cancer risk across populations. It is likely that obesity may thus provide a link between westernization and increased prostate cancer risk. With the epidemic of obesity in both developed and developing countries, the role of obesity needs to be clarified further.

Physical Activity

Physical activity may decrease levels of total and free testosterone, reduce obesity, and enhance immune function,[40] all of which may lead to protection from prostate cancer. However, perhaps due to challenges in classifying physical activity and/or identifying the age/time period at which

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activity may be most protective, results from numerous epidemiologic studies are equivocal.[40,41]

Occupation

Occupation is highly correlated with socioeconomic status and lifestyle factors. There is a large body of literature on prostate cancer and occupation, and one consistent result from these studies is that farmers and other agricultural workers have a 7–12% increased risk.[42,43] While this excess could reflect lifestyle factors such as increased intake of meat and fats, chemical exposures may also play a role. These chemicals, which have a wide variety of poorly characterized effects, may include fertilizers, solvents, pesticides and herbicides.[44] Organochlorines present in many pesticides and herbicides can affect circulating hormone levels; however the epidemiologic evidence linking specific pesticide or herbicide exposures to prostate cancer is weak. In addition to agriculture, workers in the heavy metals industry, rubber manufacturing, and newspaper printing may be at elevated risk,[42] suggesting that exposure to certain chemicals common in these work environments may increase the risk of prostate cancer.

Vasectomy

Several, but not all, studies investigating the association between vasectomy and prostate cancer risk suggest a modest positive association. The role of vasectomy remains controversial, however, since most studies are unable to exclude the possible effect of detection bias: men undergoing vasectomies are more likely to have prostate cancer detected than men who do not. Vasectomy is linked to elevations in anti-spermatozoa antibodies, decreased seminal hormone concentrations and decreased prostatic secretion.[45] Whether these conditions can influence prostate carcinogenesis needs to be clarified.

Chronic Inflammation

Evidence for chronic inflammation and prostate cancer is just emerging,[46] but an association of prostate cancer with chronic inflammation of the prostate (chronic prostatitis) has long been suspected. Inflammation is frequently found in prostate biopsy specimens obtained from both radical prostatectomy and surgical treatment for BPH,[47,48] however, epidemiologic findings have been mixed. A recent meta-analysis of 11 studies of prostatitis and prostate cancer reported an overall relative risk of 1.6.[49]

Results from pathologic and molecular surveys suggest that the earliest stages of prostate cancer may develop in lesions generally associated with chronic inflammation.[50,51] De Marzo *et al.* showed that almost all forms of focal prostatic glandular atrophy, thought to be precursors of prostatic adenocarcinoma, are proliferative, and that such proliferative inflammatory atrophy (PIA) lesions often contain inflammatory infiltrates and are frequently found adjacent to or near high-grade prostatic intraepithelial neoplasia (PIN).[50,51] Inflammation may lead to tumorigenesis by stimulating angiogenesis, enhancing cell proliferation, and damaging DNA through radical oxygen species such as nitric oxide.

Additional support for a role for chronic inflammation in prostate cancer comes from the observation that a higher intake of fish and use of aspirin and other non-steroidal anti-inflammation drugs (NSAIDs) has been associated with reduced prostate cancer risk.[52] In two large prospective studies, higher intake of fish was associated with a lower risk of total prostate cancer and metastatic prostate cancer.[53,54] Abundant in fatty fish, omega-3 fatty acids are known antagonists of arachidonic acid and suppress the production of pro-inflammatory cytokines.[55] In addition, use of anti-inflammatory agents, especially NSAIDs such as ibuprofen or aspirin, has been related to lower prostate cancer risk in epidemiologic studies,[56–58] and a recent meta-analysis of 12 of these studies concluded that aspirin use was associated with a 15% reduction in prostate cancer risk.[59] Taken together, these data suggest chronic inflammation may increase the risk of prostate cancer. However, there are few epidemiologic studies investigating this directly, possibly due to the difficulty in diagnosing chronic prostatitis and in measuring cytokine levels reliably in serum samples. This is likely to be a fruitful area for future research.

Sexually Transmitted Diseases

Chronic inflammation induced by bacterial or viral agents has been implicated as a potential underlying mechanism for the link between STDs and prostate cancer. One recent large, population-based study showed two- to three-fold increased prostate cancer risks associated with STDs, particularly syphilis and recurrent gonorrhea infections.[60] Other studies reported associations of human papillomavirus-16, -18 and -33 serology with an increased risk of prostate cancer.[61,62] In addition, epidemiological data are accumulating to suggest that sexual history may be associated with prostate cancer risk,[63] and a recent meta-analysis of 17 studies concluded that increased sexual frequency and number of partners are associated with increased prostate cancer risk.[49]

Benign Prostatic Hyperplasia

The relationship between BPH and prostate cancer is not well established. BPH is currently not considered a precursor to prostate cancer, since prostate cancer occurs mostly in the peripheral zone of the prostate and BPH is more common in the transition and periurethral zones. However, because both conditions are common in elderly men, and because they may coexist within the prostate, they appear to share risk profiles, making it difficult to elucidate the independent role, if any, of BPH in prostate cancer etiology. Detection bias also complicates investigation: excess prostate cancer risk in men who are symptomatic for BPH may be simply a reflection of the increased intensity of evaluation and medical surveillance in such patients. In addition, in most epidemiologic studies, it has been difficult to completely rule out the presence of BPH in control populations, since the prevalence of BPH is very common in elderly men. Due in part to these limitations, the epidemiologic evidence for BPH as a risk factor for prostate cancer remains weak and inconsistent,[64] with the largest study to date (over 85,000 BPH patients) showing only a marginally elevated risk of prostate cancer versus the general population ($<2\%$ in 10 years).[65]

Other Factors

Several other risk factors, such as smoking, use of alcohol, diabetes and liver cirrhosis, have been investigated, but their roles in prostate cancer are weak or unclear based on data in the current literature.[66–68]

Genetic Factors

Family History of Cancer

Prostate cancer etiology has a hereditary component. Numerous studies have consistently reported familial aggregation of prostate cancer, showing a two- to three-fold increased risk of prostate cancer among men who have a first-degree male relative (father, brother, son) with a history of prostate cancer.[69] Recent data from a large twin study suggests that as much as 42% (95% CI 29–50%) of the risk of prostate cancer may be accounted for by genetic factors.[70] Genetic factors involved in prostate cancer include individual and combined effects of rare, highly penetrant genes, more common weakly penetrant genes and genes acting in concert with each other.

High-Penetrance Markers

Segregation and linkage analyses have shown that certain early-onset prostate cancers may be inherited in an autosomal dominant fashion,[71] and it is estimated that such hereditary prostate cancers (HPCs) due to highly penetrant genes may account for about 10% of all prostate cancer cases.[70] Several family studies are currently underway to identify hereditary prostate cancer candidate genes. However, these investigations have proven to be difficult for several reasons.[72] One is that, due to the high incidence of prostate cancer and the heterogeneity of tumors, it is possible that sporadic cases are included in HPC families, thereby reducing the statistical power to detect genes for HPC. In addition, because prostate cancer is generally diagnosed at a late age, it is often impossible to obtain DNA specimens from fathers of HPC cases, and sons of HPC cases are often too young to have developed prostate cancer. Therefore, studies of HPC families are often unable to include more than one generation. Finally, the genetic heterogeneity of prostate cancer makes it difficult to devise appropriate statistical transmission models that also account for multiple susceptibility genes, many of which may be at only moderate penetrance. Despite these challenges, seven loci have been described to date, including *HPC1, ELAC2, HPCX, HPC20, CAPB, PCAP*, and an unnamed locus at 8p22-23 (Table 2), and fine mapping has led to the identification of a number of candidate genes, including *RNASEL*, *ELAC2* and MSR-1.[73,74] The results of studies of these loci,[75–95] which have been extensively reviewed elsewhere,[73] have largely been mixed, with subsequent studies failing to replicate promising earlier findings. The absence of strong, consistent results for high penetrance markers strongly suggests that the heritable component of prostate cancer largely comprises effects of multiple factors, including common, weakly penetrant markers, possibly interacting with one another and with environmental factors.

Common Low-Penetrance Markers

Results of epidemiologic studies of common polymorphisms are summarized below and in Table 3 by biological pathway; several of these markers have been reviewed elsewhere.[73,96–99] In reviewing these results, it is important to note that, as with any other epidemiologic exposure, replication of findings is critical to establishing causality. This is particularly true of genetic association studies, because the recent explosion of genetic data has increased the potential for publication bias as investigators and publishers become more selective about writing up and publishing findings.

Androgen Biosynthesis and Metabolism Pathway

Because prostate cancer is an androgen-dependent tumor, it is likely that markers in genes whose gene products are involved in androgen biosynthesis and metabolism (Fig. 3) may be associated with disease. Recent epidemiologic studies have investigated the role of polymorphisms of over 10 genes involved in androgen biosynthesis, metabolism, transport, and regulation. These data are promising and accumulating at a remarkable pace but still are too sparse to support a role for any particular gene.

Results for the androgen receptor (*AR*), which is involved in androgen binding and transport, are fairly consistent, showing that shorter CAG repeat lengths are associated with increased risk in most, but not all, populations.[100–119] For the type II steroid 5α-reductase (*SRD5A2*), which converts testosterone to the more active androgen dihydrotestosterone, the results are mixed,[110,119–133] with a recent meta-analysis showing modest

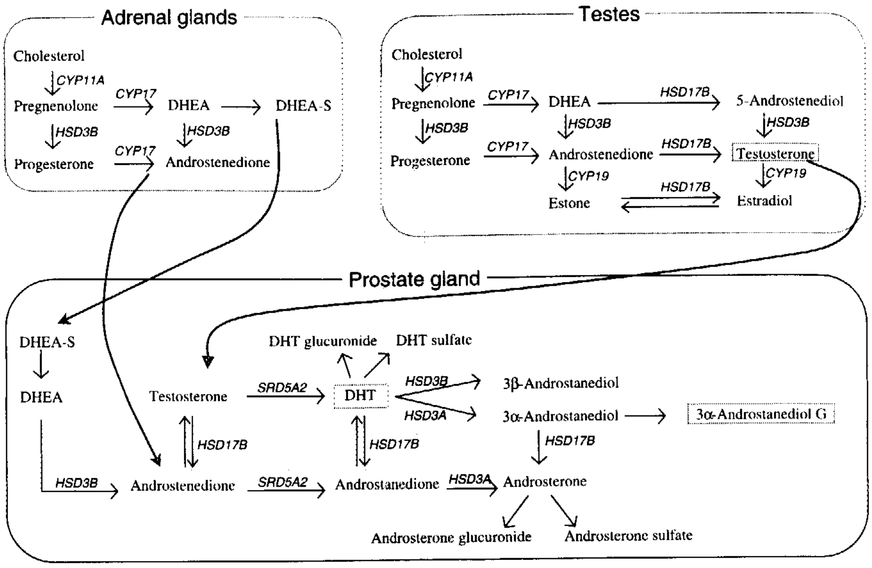

Fig. 3. Androgen biosynthesis and metabolism pathway.

risk increases associated with shorter TA repeats and the T allele of the A49T marker, but not for other studied markers.[96] Markers in several other genes, including cytochrome p450-17 (*CYP17*), cytochrome p450-19 aromatase (*CYP19*), cytochrome p450-1A1 (*CYP1A1*) and cytochrome p450-3A4 (*CYP3A4*) have shown promising initial results that often cannot be replicated.[110,111,119,120,125,134–148] Furthermore, recent initial studies of 17β-hydroxysteroid dehydrogenase 3 (*HSD17B3*) and 3β-hydroxysteroid dehydrogenase 1 (*HSD3B1*) have shown promising results,[149,150] but further study is needed to elucidate the role these may play in prostate cancer.

The totality of current data suggests that racial/ethnic variation exists in polymorphisms of genes involved in the androgen pathways.[151,152] However, their role in prostate cancer needs to be clarified further.

Growth Factor and Non-Androgenic Hormone Pathways

Due to serological evidence linking them to prostate cancer, a number of studies have explored the prostate cancer risk associated with polymorphic markers in genes involved in the insulin and insulin-like growth factor (IGF) signaling pathway. However, while the only study of the insulin gene (*INS*) has shown promising results, early studies of markers in the IGF-II and IGF binding protein-3 (IGFBP-3) genes have shown null results.[94,119,153]

Strong laboratory evidence showing chemoprotection of vitamin D against prostate cancer, in addition to suggestive but inconsistent sero-epidemiological studies, has led to numerous studies of the vitamin D receptor gene (*VDR*).[100,119,154–166] However, despite promising early studies, a recent comprehensive meta-analysis showed no overall associations and concluded that markers in the *VDR* gene are unlikely to be major genetic determinants of prostate cancer risk.[97]

Carcinogen Metabolism Pathway

Genes encoding enzymes that metabolize carcinogens and other toxins may play a role in prostate cancer. However, results from several studies of markers in different glutathione-*S*-transferases (GSTs), including *GSTT1*, *GSTP1* and *GSTM1*, have mostly been null.[76,119,134,167–175] Recent initial epidemiologic studies of other genes in these pathways, including *GSTM3* and *N*-acetyl transferase 2 (*NAT2*), have been positive but require confirmation.[134,167]

DNA Repair Pathway

The DNA repair pathway serves to prevent disruptions in DNA integrity that might otherwise lead to gene rearrangements, translocations, amplifications and deletions that may contribute to cancer development.[176] Initial reports of markers in genes encoding DNA repair enzymes, including the X-ray repair cross-complementing group (*XRCC1*), human 8-oxoguanine glycosylase I (*hOGG1*) and the xeroderma pigmentosum group D (*XPD*), show promising results.[177–180] These results, combined with strong biological plausibility, suggest that this may be a fruitful area for further research.

Chronic Inflammation Pathway

Several lines of evidence point to a role of inflammation in prostate cancer etiology, and studies of markers in the genes involved in inflammation are emerging.[46] Initial studies show positive results for transforming growth factor-β (*TGF-β*) and COX-2[181,182] and negative results for tumor necrosis factor-α-308 (*TNF-α-308*), interleukin-1β (*IL-1β*) and peroxisome proliferator-activated receptor-γ (*PPAR-γ*).[183,184] Evidence for a role of inflammation markers in prostate cancer is increasing. Given the biological plausibility of this hypothesis, this should be a fruitful area for future research.

Angiogenesis Pathways

The need for increased vasculature to support cancer growth is an area of research that is currently gaining momentum. Genetic investigations of angiogenesis in prostate cancer have thus far involved the vascular endothelial growth factor (*VEGF*) gene as well as the genes for *IL-8* and *IL-10*, and the handful of studies conducted to date have shown positive results.[142,183] These findings await further confirmation and support the notion that angiogenesis may indeed be involved in prostate cancer.

Biological Pathways Related to Dietary Factors

It is clear that genetic susceptibility to both Phase I and II enzymes (cytochrome p450) affects the association between certain dietary factors and prostate cancer risk. For example, the effect of cruciferous vegetables is related to both their high glycosinolate content and functional variations in enzymes, particularly *GSTM1* and *GSTT1*, that metabolize glycosinolates to isothiocyanates (ITCs).[27] Thus, to better assess the role of ITCs in prostate cancer, studies with both comprehensive and reliable assessment of cruciferous vegetable intake and genetic polymorphisms in *GSTM1* and *GSTT1* will be required. Moreover, genetic polymorphisms in receptors and transcription factors that interact with these compounds may contribute to variations in response to cruciferous vegetable intake. With sufficiently large sample size and careful assessment of diet and genetic factors, this important area should be investigated further.

Challenges of Studies with Common Polymorphisms

Currently, the totality of data suggests that racial/ethnic variation exists in common polymorphisms of certain genes, such as the *SRD5A2, AR*, and

ELAC2/HPC2, but few variants or genes have been firmly shown to contribute to prostate cancer susceptibility. Challenges in molecular epidemiology studies of common polymorphisms include the selection of relevant single nucleotide polymorphisms (SNPs) for genotyping and the difficulty in replicating results. The difficulty in replicating earlier findings in subsequent association studies is due, in part, to (1) the relatively small to modest effects of most common polymorphisms, ranging from 10 to 80%, (2) the relatively small sample size in most previous studies, ranging from 100 to 500 cases, and the limited power of these studies to detect a modest effect on the order of 10 to 50%, (3) the tendency of small studies to produce false positive findings, and (4) differences in study design and populations, including differences in the severity of cases. Thus, studies with large sample size (>1000 cases) are needed to clarify further the role of these polymorphic markers. In addition, it is becoming clear that a single gene or SNP alone is unlikely to explain most of the variation in prostate cancer susceptibility, thereby requiring even larger sample sizes (>3000 cases) to evaluate the effect of multiple variants.

Another challenge in epidemiologic studies investigating the role of genetic variants in complex disease (e.g., prostate cancer) is the limited ability to identify "causal SNPs" through association studies. This is partly related to two factors, (1) the difficulty in selecting biologically relevant SNPs for genotyping and (2) the inability to tease out causal SNPs from blocks of SNPs that are in high linkage disequilibrium (LD). For each gene of interest, there may be a dozen to a few hundred SNPs. The conventional approach is to choose SNPs with functional significance for genotyping. This is a difficult task in practice, given the very large pool of known SNPs and the limited information on the functional significance of many SNPs. In some studies, a haplotype-tagging approach has been used to identify informative SNPs by exploiting blocks of SNPs that are in high LD.[185–187]

Rapid progress in molecular epidemiology during the next few years is likely to hinge upon several factors, including the availability of large well-designed interdisciplinary epidemiologic studies, development of novel approaches, and statistical methods to deal with the vast amount of data, and innovative laboratory methods, such as DNA pooling[188] or whole genome scans, that permit typing multiple genetic markers at a much lower cost with higher throughput.

It is clear that prostate cancer etiology involves an intricate interplay between lifestyle and genetic factors. To fully explore the complexity of interrelationships between the numerous elements in these pathways will require large cohort studies in which blood is sampled prior to diagnosis. Such studies will be important for identifying which modifiable aspects of lifestyle (such as diet, obesity, and physical activity) can be targeted for prevention and risk reduction. To this end, studies such as the Cohort Consortium, a collaborative agreement launched in 2003 involving over 10 large, prospective cohorts with a combined total of over 7000 incident prostate cancer cases, have been organized to provide unique opportunities to evaluate the complex relationships between lifestyle and genetics in prostate cancer etiology with sufficient statistical power.

The widespread use of PSA testing in western populations has changed the characteristics of cases included in epidemiologic studies.[189] Prostate cancer cases diagnosed in the PSA era are more likely to have early lesions, which may differ in etiology from advanced lesions and more aggressive tumors. This is frequently reflected in recent epidemiologic investigations that include a large number of cases with both early and advanced lesions, which frequently show positive associations for advanced stage or more aggressive tumors but not for early stage or localized tumors. It is important that future studies include prostate tumor subclassification, such as methods of detection, markers of biological aggressiveness, and genetic changes, in order to provide more accurate risk estimates related to specific risk factors.

Summary

Epidemiologic observations provide important clues to the etiology of prostate cancer. Although the causes of prostate cancer remain unclear, there are many intriguing leads, including both environmental and genetic factors. The pathogenesis of prostate cancer reflects complex interactions between several environmental and genetic factors. With newly available tools in molecular biology and genomics, a new generation of large-scale multidisciplinary population-based studies is beginning to investigate the individual and combined effects of environmental and genetic factors. These studies are likely to provide unique information on risk factors and

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